

wherein:

R¹ is selected from H; -C₁₋₄alkyl; -CO-C₁₋₄alkyl; -CO-O-C₁₋₄alkyl; -CO-O-C₂₋₄alkenyl; -C₁₋₄alkylene-CONR⁴R⁵ (wherein R⁴ and R⁵ are independently selected from H and C₁₋₄alkyl); -C₁₋₄alkylene-COOR⁶ (wherein R⁶ is selected from H and C₁₋₄alkyl); -C₁₋₃alkylene-Ph and -CO-O(CH₂)_nPh wherein the phenyl groups in -C₁₋₃alkylene-Ph and -CO-O(CH₂)_nPh are optionally substituted by R^a and/or R^b and R^a and R^b are independently selected from C₁₋₄alkyl, halogen, hydroxy, C₁₋₄alkoxy, C₁₋₄alkanoyl, C₁₋₄alkanoyloxy, amino, C₁₋₄alkylamino, di(C₁₋₄alkyl)amino, C₁₋₄alkanoylamino, nitro, cyano, carboxy, carbamoyl, C₁₋₄alkoxycarbonyl, thiol, C₁₋₄alkylsulfanyl, C₁₋₄alkylsulfinyl, C₁₋₄alkylsulfonyl and sulfonamido; and n=0-4;

R² is selected from H; -C₁₋₄alkyl; -COC₁₋₄alkyl; and -COOC₁₋₄alkyl; and

-C₁₋₃alkylene-Ph optionally substituted on the phenyl ring by R^a and/or R^b;

R³ is selected from H; OH; CN; CF₃; NO₂; -C₁₋₄alkyl; -C₁₋₄alkylene-R⁷;

-C₂₋₄alkenylene-R⁷; -C₂₋₄alkynylene-R⁷; R⁷; OR⁷ (where R⁷ is selected from phenyl, naphthyl,

a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms

selected from O, N and S and any aryl ring in R⁷ is optionally substituted by R^a and/or R^b);

C₂₋₄alkenyl; halogen; -(CH₂)_yCOOR⁸ (where y = 0-3 and R⁸ represents H, C₁₋₄alkyl, or

C₂₋₄alkenyl); -CONR⁹R¹⁰ (where R⁹ and R¹⁰ independently represent H, C₁₋₄alkyl,

C₂₋₄alkenyl, -O-C₁₋₄alkyl, -O-C₂₋₄alkenyl or -C₁₋₃alkylenePh (wherein Ph is optionally

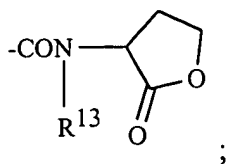
substituted by R^a and R^b as hereinabove defined); -CON(R¹¹)OR¹² (where R¹¹ and R¹²

independently represent H, C₁₋₄alkyl or C₂₋₄alkenyl);

a group of Formula II: -CONR¹³-CR^{13a}R¹⁴-COOR¹⁷, (where R¹³ and R^{13a} are independently

H or C₁₋₄alkyl, R¹⁷ is H or C₁₋₆alkyl, R¹⁴ is selected from the side chain of a lipophilic amino

acid, carbamoylC₁₋₄alkyl, N-(monoC₁₋₄alkyl)carbamoylC₁₋₄alkyl and N-(diC₁₋₄alkyl)carbamoylC₁₋₄alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula:

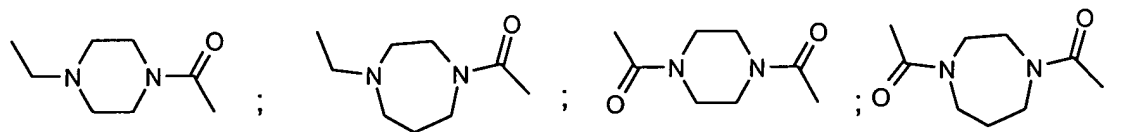


C₁₋₄alkyl monosubstituted on carbon with =N-OH;

a group of Formula -X-R¹⁵ (where X is selected from O, CO, CH₂, S, SO, SO₂ and R¹⁵ is selected from C₁₋₆alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R¹⁵ is optionally substituted by R^a and/or R^b;

p is 0-3 in which R³ values can be the same or different;

G is a linking moiety selected from the following groups written from left to right in Formula I:



(wherein the piperazine and perhydro-1,4-diazepine rings are optionally substituted);

-CO-NR¹⁶-; -CH₂-NR¹⁶-; -CH₂S-; -CH₂O-; -CH₂-CHR¹⁶; -CH=CR¹⁶-; -CH₂NR¹⁶-T-; -CH₂NR¹⁶-SO₂-; -CH₂-NR¹⁶-CO-T¹-; -CO-NR¹⁶-T-; -CH₂S-T-; -CH₂O-T- (where R¹⁶ is selected from H, C₁₋₄alkyl, C₁₋₄alkylene-Z, -CO-C₁₋₄alkylene-Z, -CO-C₁₋₆alkyl, -COZ, Z and Z is selected from -O-C₁₋₄alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R¹⁶ is optionally substituted by R^a and/or R^b as hereinabove defined;

where, T represents -(CH₂)_m- where m is 1-4 and T is optionally monosubstituted with any value of R¹⁶ other than H; and

where T¹ represents -(CH₂)_m¹- wherein m¹ is 0-4 and T¹ is optionally monosubstituted with any value of R¹⁶ other than H);

01 A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N & S;
or a -S-S- dimer thereof when $R^2=H$; or a N-oxide thereof;
or a pharmaceutically acceptable salt, prodrug or solvate thereof.

Please further amend the first paragraph on page 4, line 10 to page 6, line 11, as follows:

(Twice Amended) In another aspect of the invention there is provided an inhibitor of ras farnesylation of Formula I

wherein:

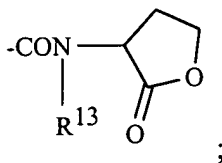
02 R^1 is selected from H; $-C_{1-4}alkyl$; $-C_{1-3}alkylene-Ph$ optionally mono or di-substituted on Ph with substituents selected from $C_{1-4}alkyl$, halogen, OH, $C_{1-4}alkoxy$, $C_{1-4}alkanoyl$, $C_{1-4}alkanoyloxy$, amino, $C_{1-4}alkylamino$, $di(C_{1-4}alkyl)amino$, $C_{1-4}alkanoylamino$, nitro, cyano, carboxy, carbamoyl, $C_{1-4}alkoxycarbonyl$, thiol, $C_{1-4}alkylsulfanyl$, $C_{1-4}alkylsulfanyl$, $C_{1-4}alkylsulfonyl$ and sulfonamido; $-CO-C_{1-4}alkyl$; $-CO-O-C_{1-4}alkyl$; $-CO-O-C_{2-4}alkenyl$; $-CO-O-(CH_2)_nPh$ optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}alkylene-Ph$ above and $n=0-4$;
 $-C_{1-4}alkylene-CONR^4R^5$ where R^4 & R^5 are independently selected from H and $C_{1-4}alkyl$; and $-C_{1-4}alkylene-COOR^6$ where R^6 is selected from H, $C_{1-4}alkyl$;
 R^2 is selected from H; $-C_{1-4}alkyl$; $-C_{1-3}alkylene-Ph$ optionally substituted on Ph as defined for substitution on Ph in $R^1 = -C_{1-3}alkylene-Ph$ above; $-COC_{1-4}alkyl$; and $-COOC_{1-4}alkyl$;
 R^3 is selected from H; OH; CN; CF_3 ; NO_2 ; $-C_{1-4}alkyl$; $-C_{1-4}alkylene-R^7$ where R^7 is selected from phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in R^7 is optionally substituted as defined for substitution on the Ph group in $R^1 = -C_{1-3}alkylene-Ph$ above; R^7 ; $C_{2-4}alkenyl$; halogen; $-(CH_2)_yCOOR^8$ where $y=0-3$ and R^8 represents H, $C_{1-4}alkyl$, or $C_{2-4}alkenyl$;
 $-CONR^9R^{10}$ where R^9 and R^{10} independently represent H, $C_{1-4}alkyl$, $C_{2-4}alkenyl$, $-O-C_{1-4}alkyl$, $-O-C_{2-4}alkenyl$, $-C_{1-3}alkylenePh$ optionally substituted as defined for this group

for R^1 above; $-\text{CON}(R^{11})\text{OR}^{12}$ where R^{11} and R^{12} independently represent H, C_{1-4} alkyl and C_{2-4} alkenyl;

a group of Formula II, $-\text{CONR}^{13}-\text{CHR}^{14}-\text{COOR}^{17}$, where R^{13} is H or C_{1-4} alkyl, R^{17} is H or C_{1-6} alkyl, R^{14} is selected from the side chain of a lipophilic amino acid,

carbamoyl C_{1-4} alkyl, N-(mono C_{1-4} alkyl)carbamoyl C_{1-4} alkyl and

N-(di C_{1-4} alkyl)carbamoyl C_{1-4} alkyl, the group of Formula II having L or D configuration at the chiral alpha carbon in the corresponding free amino acid; a lactone of formula



C_{1-4} alkyl monosubstituted on carbon with $=\text{N}-\text{OH}$;

a group of Formula $-\text{X}-\text{R}^{15}$ where X is selected from O, CO, CH_2 , S, SO, SO_2 and R^{15} is

selected from C_{1-6} alkyl, phenyl, naphthyl, a 5-10 membered monocyclic or bicyclic

heteroaryl ring containing up to 5 heteroatoms selected from O, N and S and any aryl ring in

R^{15} is optionally substituted as defined for the Ph group in $R^1 = -\text{C}_{1-3}$ alkylene-Ph;

p is 0-3 in which R^3 values can be the same or different;

G is a linking moiety selected from the following groups written from left to right in

Formula I:

$-\text{CO}-\text{NR}^{16}-$ where R^{16} is selected from H, C_{1-4} alkyl, C_{1-4} alkylene-Z, $-\text{CO}-\text{C}_{1-4}$ alkylene-Z,

$-\text{CO}-\text{C}_{1-6}$ alkyl, $-\text{COZ}$, Z and Z is selected from $-\text{O}-\text{C}_{1-4}$ alkyl, phenyl, naphthyl, a 5-10

membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms selected

from O, N and S and any aryl ring in R^{16} is optionally substituted as defined for the Ph group

in $R^1 = -\text{C}_{1-3}$ alkylene-Ph; $-\text{CH}_2-\text{NR}^{18}-$ where R^{18} represents any value defined for R^{16} ;

$-\text{CH}_2\text{S}-$; $-\text{CH}_2\text{O}-$; $-\text{CH}_2-\text{CHR}^{19}-$ where R^{19} represents any value defined for R^{16} ; $-\text{CH}=\text{CR}^{20}-$

where R^{20} represents any value defined for R^{16} ; $-\text{CH}_2\text{NR}^{21}-\text{T}-$ where R^{21} represents any value

defined for R^{16} , T represents $-(\text{CH}_2)_w-$ where w is 1-4 and T is optionally monosubstituted

with R^{22} where R^{22} represents any value for R^{16} other than H; $-\text{CH}_2\text{NR}^{23}-\text{SO}_2-$ where R^{23}

represents any value defined for R^{16} ; $-\text{CH}_2-\text{NR}^{24}-\text{CO}-\text{T}-$ where R^{24} represents any value

defined for R^{16} , T represents $-(\text{CH}_2)_w-$ where w is 0-4 and T is optionally monosubstituted

0² with R²⁹ where R²⁹ represents any value for R¹⁶ other than H; -CO-NR²⁵-T- where R²⁵ represents any value defined for R¹⁶, T represents -(CH₂)_w- where w is 1-4 and T is optionally monosubstituted with R²⁶ where R²⁶ represents any value for R¹⁶ other than H; -CH₂S-T- where T represents -(CH₂)_w- where w is 1-4 and T is optionally monosubstituted with R²⁷ where R²⁷ represents any value for R¹⁶ other than H; -CH₂O-T- where T represents -(CH₂)_w- where w is 1-4 and T is optionally monosubstituted with R²⁸ where R²⁸ represents any value for R¹⁶ other than H;

A is selected from phenyl; naphthyl; a 5-10 membered monocyclic or bicyclic heteroaryl ring containing up to 5 heteroatoms where the heteroatoms are independently selected from O, N & S;

or a -S-S- dimer thereof when R²=H; or a N-oxide thereof;

or an enantiomer, diastereoisomer, pharmaceutically acceptable salt, prodrug or solvate thereof.

Please further amend the first paragraph on page 10, line 4 to page 10, line 15, as follows:

(Twice Amended) Suitable values for G= CH₂NR¹⁶ T include

0³ CH₂N(CO.CH₂.CHMe₂).CH₂.CH₂; CH₂N(CH₂ CH₂ CH₂OMe).CH₂.CH₂;
 CH₂N(CH₂.pPh.OMe).CH₂.CH₂; CH₂N(CO.CH₂.CHMe₂).CH₂;
 CH₂N(CO.CH₂.CH₂.CH₂.Me).CH₂; CH₂N(CO.CH₂.CHMe.CH₂Me).CH₂;
 CH₂N(CO.CH₂.CH₂.OMe)CH₂; CH₂N(CO.CH₂.pyridin-3-yl).CH₂;
 CH₂N(4-methoxybenzyl)CH₂; CH₂N(CO.CH₂.CHMe₂)CH₂.CH₂.CH(Ph);
 CH₂N(CO.CH₃)CH₂.CH₂.CH(Ph); CH₂N(CO.CH₂.CHMe₂)CH₂; CH₂N(CO.CH₃)CH₂;
 CH₂N(CO.CH₂.CHMe₂)CH₂.CH(Ph); CH₂N(CO.CH₂.CMe₃)CH₂.CH(Ph);
 CH₂N(CO.CH₂.pyridin-3-yl)CH₂.CH(Ph);
 CH₂N(CO.1-hydroxy-6-methoxy-pyridin-3-yl)CH₂.CH(Ph);
 CH₂N(CO.CH₂ pyrid-3-yl)CH₂CH(Ph); CH₂N(CO.CH₂CHMe₂)CH₂.CH₂;
 CH₂N(CO.CH₂CMe₃)CH₂.CH₂; CH₂N(CO thiazol-2-yl)CH₂CH₂; CH₂N(CO 1-oxido-6-hydroxypyridin-3-yl)CH₂CH₂; CH₂N(CO.CH₂pyridin-3-yl)CH₂.CH₂ and
 CH₂N(CO.4-methoxybenzyl)CH₂.CH₂.

Please further amend the third paragraph on page 10, line 20 to page 10, line 22, as follows:

04 (Twice Amended) Suitable values for $G = -CH_2NR^{16}$ include CH_2NH ; CH_2NMe ; $CH_2N(CO.CH_2.CHMe_2)$ and $CH_2N(CO.CH_2.CH_2.OMe)$. A preferred value for $-CH_2NR^{16}$ is $-CH_2NH-$.

Please further amend the fourth paragraph on page 10, line 23 to page 10, line 26 as follows:

05 (Twice Amended) When G is $-CH_2NR^{16}-T-$ a suitable value for m is 1. When G is $-CH_2-NR^{16}-CO-T^1-$ a suitable value for m^1 is 1. When G is $-CH_2-NR^{16}-T-$ a suitable value for m is 1. When G is $-CH_2-S-T-$ a suitable value for m is 1. When G is $-CH_2-O-T-$ a suitable value for m is 1.

G is especially $-CONH-$, $-CH_2-NH-$, $-CH_2NHSO_2-$, $-CH_2NHCO-$.

Please further amend the first paragraph on page 32, line 4 to page 32, line 23, as follows:

06 (Twice Amended) Compounds of Formula I in which G represents $-CO-NR^{16}$ may be prepared by forming an amide bond between compounds 1 and 2 as outlined in Scheme 1. Compounds of Formula I in which G represents $-CO-NR^{16}-T-$ may be prepared by an analogous procedure. Suitable coupling conditions include the following.

- i) Use of EEDQ at ambient temperature in an organic solvent (e.g. dichloromethane, methanol).
- ii) Use of oxalyl chloride in an organic solvent (e.g. CH_2Cl_2), DMF in a catalytic amount, in the presence of an organic base (e.g. NMM, triethylamine, DMAP) at $0^\circ C$ to ambient temperature for 0.5-16h.
- iii) Use of EDC/ HOBT in an organic solvent (e.g. DMF, CH_2Cl_2).
- iv) Use of DCCI/ HOBT in an organic solvent (e.g. DMF, CH_2Cl_2) in the presence of an organic base (e.g. triethylamine).

06 v) Use of mixed anhydride reactions under standard conditions, for example isopropylchloroformate in an organic solvent (e.g. DMF, DMA, dichloromethane) in the presence of an organic base (e.g. NMM, DMAP, triethylamine).

vi) Via an active ester under standard conditions e.g. pentafluorophenyl ester in an organic solvent (e.g. dichloromethane) in the presence of an organic base (e.g. triethylamine).

vii) Via an acid chloride under standard conditions e.g. using thionyl chloride and heat for about 150min followed by an organic base (e.g. triethylamine) in the presence of an organic solvent (e.g. acetonitrile).

Please further amend the second paragraph on page 32, line 24 to page 33, line 3, as follows:

(Twice Amended) Compounds of Formula I in which G represents $-\text{CH}_2\text{NR}^{16}-$, $-\text{CH}_2\text{O}-$ or $-\text{CH}_2\text{S}-$ may be prepared as outlined in Scheme 2. LG represents a leaving group (e.g. mesyloxy, tosyloxy, halogen) and X represents S, O or NR^{16} . Suitable coupling conditions include the following.

07 i) Use of an inorganic base (e.g. NaHCO_3 , NaH, K_2CO_3 , butyllithium) in an organic solvent (e.g. THF, DMF, DMSO) and a temperature of about 65° to 150°C

ii) Use of an organic base (e.g. triethylamine, DMAP) in an organic solvent (e.g. THF, dichloromethane, DMA, DMF) at a temperature range of room temperature - 150°C

iii) Use of an inorganic base (e.g. KOH, NaOH, K_2CO_3) in an aqueous (e.g. water) and organic solvents (e.g. dichloromethane) in a 2 phase system, optionally in the presence of a phase transfer catalyst (e.g. tetrabutylammoniumbromide).

Please further amend the second paragraph on page 33, line 13 to page 33, line 18, as follows:

08 (Twice Amended) Compounds of Formula I in which G represents $-\text{CH}_2-\text{NR}^{16}-$ may be prepared as outlined in Scheme 4 by coupling aldehyde (2) with compound 4. Suitable coupling conditions include the following.